

Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

REMARKS

Claims 1, 3-5, 14-34, and 37-41 are pending in the present application. Among them, Claims 3, 28, and 29 are directed to non-elected species, and are withdrawn from further consideration.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Application Status

In the instant Office Action Summary page, both the "Final Office Action" and "non-Final Office Action" boxes are checked. In an attempt to clarify the application status, Applicants' attorney Yu Lu called Examiner on February 1, 2008, and inquired the status of this Office Action. The Examiner clarified that Applicants should treat this action as a **non-Final Office Action**. Applicants' attorney acknowledged that Applicants will note this for the record in the instant response.

Claim Rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 38-40 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. However, in supporting the rejection, the Examiner reiterated reasons pertaining to the rejection of the canceled Claims 35 and 36, and hardly offered any applicable reasons to support the rejection of Claims 38-40.

Thus, Applicants assume that the Examiner has (mistakenly) maintained the rejection to canceled claims 35 and 36. If this is the case, Applicants respectfully request the Examiner to withdraw the rejection to Claims 38-40.

If the Examiner, however, insists to maintain the rejection to Claims 38-40, Applicants note that the Examiner's previous argument (*i.e.*, that "reversible inhibitors are not likely available for many proteases") seems to be contradictory to the evidence Applicants have previously provided. In addition, the Examiner has failed to provide any affidavit or declaration

Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

required under 37 C.F.R. § 1.104(d)(2).

Applicants wish to remind the Examiner that “[i]f applicant adequately traverses the examiner’s assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. *See* 37 C.F.R. 1.104(c)(2). *See also Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697 (“[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings” to satisfy the substantial evidence test).” *See* MPEP 2144.03, Section C.

In view of the foregoing, Applicants submit that all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The Office Action maintains the rejection to Claims 1, 4, 14, 16-25, 30-41 under 35 U.S.C. § 102 as allegedly being anticipated by Davis *et al.* (WO 00/64485, “Davis”).

In response to Applicants’ previous argument that Davis does not teach a fusion protein, the Office Action maintains the rejection by continually relying on a wrong interpretation of the term “fusion protein.” Specifically, although the Examiner has acknowledged that “David et al. fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent” (emphasis added, see page 6 in the instant Office Action), the Examiner insists that such chemically cross-linked complexes are also “fusion proteins.” The Examiner further states that “[f]usion of two or more proteins or polypeptides via chemically [sic] or recombinantly [sic] form [sic] a ‘fusion’ protein.”

Applicants reiterate that chemically cross-linked two or more polypeptides are not a single “fusion protein” within the scope of the claims.

To support Applicants’ position, Applicants hereby submit several definitions for “fusion protein” as used by one of skill in the art. None of these definitions supports the Examiner’s interpretation of the term “fusion protein.”

For example, the U.S. NCI (National Cancer Institute) Dictionary of Cancer Terms

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Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

defines "fusion protein" as "A protein created by joining two genes together. Fusion proteins may occur naturally or can be created in the laboratory for research." *See Exhibit A*. Thus, a fusion protein must be a single polypeptide, and cannot be two or more polypeptides joined together by non-peptide bonds, such as chemical cross-linking taught in Davis. Furthermore, the fusion protein is encoded by two (or more) genes, which production requires transcription and translation of the joined genes. The chemically cross-linked peptides of David cannot be directly created by transcription and translation from any genes. Rather, they must be created post-translationally by manipulating separately transcribed/translated polypeptides.

Consistent with this, the online encyclopedia Wikipedia defines fusion proteins as "proteins created through the joining of two or more genes which originally coded for separate proteins. *See Exhibit B*. Translation of this fusion gene results in a single polypeptide with function properties derived from each of the original proteins" (emphasis added).

Furthermore, the Dictionary of Cell & Molecular Biology (Lackie and Dow, eds., Academic Press; 3rd edition, October 15, 1999) defines fusion protein as "protein formed by expression of a hybrid gene made by combining two gene sequences." *See Exhibit C*. Thus, as argued above, the chemically cross-linked Davis proteins cannot be formed by expression of a hybrid gene, and thus do not fall within the scope of "fusion protein" as understood by one of skill in the art and as used in the instant claims.

Finally, Davis itself supports Applicants' interpretation. For example, on page 21, lines 5-7, Davis reads "[t]he chimeric molecules of this invention offer a number of other advantages. Because they are chemically conjugated using a 'standard' chemistry, they are easier to make and/or to vary" (emphasis added). On page 22, lines 29-31, Davis reads "... the retargeted enzymes and catalytic antagonists are created by selecting a targeting moiety, selecting an enzyme (an effector moiety) and chemically conjugate the two to form a chimeric molecule" (emphasis added). Clearly, the "chimeric molecule" of Davis does not include any "fusion protein" created by transcription / translation from a chimeric gene (or a single polynucleotide).

If the Examiner insists that "fusion protein" can be used to described chemically cross-linked two or more polypeptides, Applicants respectfully request the Examiner to provide

Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

evidence (such as usage in scientific literatures) to support his argument.

In summary, Applicants submit that Davis fails to teach a "fusion protein" as recited in the claimed invention, and thus cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 103

The Office Action maintains the rejection to Claims 1, 4, 14-17, 18-27, 30-38, and 41 under 35 U.S.C. § 103(a) as allegedly being obvious in view of Davis (*supra*) or Guo *et al.* (*Biotech. and Biong* 70: 456-463, 2000, or "Guo") in view of Sallberg *et al.* (U.S. Pat. No. 6,960,569) or Whitcomb (*supra*).

Specifically, the Examiner argues that Davis teaches a fusion protein; Guo teaches a fusion protein with a (Gly₄Ser)₃ linker; Whitcomb teaches mesotrypsin, which is resistant to PSTI inhibition; and Sallberg teaches "fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolytic cleavage)."

Thus, the Examiner concludes that "... it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is resistant to trypsin inhibitor as taught by Whitcomb *et al.* or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo *et al.* to target domain as thought [sic] by Davis ... and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of [sic] the said substrate polypeptide."

In maintaining the rejection, the Office Action fails to address many of the key issues Applicants raised in the previous response. Thus Applicants submit that the rejections should be withdrawn.

Specifically, as argued above, Applicants have provided ample evidence that the term "fusion protein" does not include chemically cross-linked two or more polypeptides, as taught in Davis, and the Examiner has not provided any evidence to the contrary. Thus, contrary to the

Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

Examiner's assertion, Davis fails to teach any fusion protein.

Because Davis specifically requires the use of chemical cross-linking to connect two functional domains, Davis cannot be modified by Guo to include the (Gly₄Ser)₃ linker, because doing so would change the principle of operation in Chen and Davis. Pursuant to MPEP 2143.01: "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A., 1959)." **The Examiner has not addressed this argument.**

Secondly, even if Davis is modified by Whitcomb to include a mesotrypsin domain as its protease domain, the combined teaching at best relates to a mesotrypsin domain chemically cross-linked to a targeting domain, and thus still fails to teach any fusion protein, and cannot render the claimed invention obvious.

The same argument applies to Sallberg.

Regarding Sallberg, the Examiner states that "Applicants [sic] argument that Sallburg et al. does not teach that their NS3/4A is not [sic] resistant to auto cleavage is not found to be true because as shown (paragraph 11) in the [sic] their specification NS3/4A mutant lack [sic] proteolytic site and therefore lack [sic] proteolysis cleaving properties."

Applicants submit that the Examiner has misunderstood Applicants arguments. Applicants do not necessarily dispute that the NS3/4A mutant lacks proteolytic site. Rather, Applicants are arguing that **it is unclear whether the mutation occurs within the NS3 Ser protease domain or elsewhere in the NS3/4A fusion**. In fact, the mutation most likely does not occur within the NS3 protease domain, since the protease resistant site is between the NS3 and NS4A fusion parts (see Example 3 (col. 14)). **The Examiner has not refuted this argument.**

Applicants have also argued previously that there is not any disclosure in Sallberg that relates to conjugating the NS3/4A fusion protein to antibody or other protein, as the Office Action alleges. Sallberg relates to the identification of a new NS3/4A fusion of the HCV virus, its truncation mutants, or its mutations that lack a proteolytic cleavage site. *See* col. 3, lines 30-50. Sallberg contemplates the use of such HCV peptides as immunogens to generate antibodies

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Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

against NS3 (*see* col. 3, last paragraph). Applicants, however, were unable to find any disclosure about any conjugates of such NS3/4A fusion to any antibodies or other proteins. If the Examiner wishes to maintain this rejection, Applicants respectfully invite the Examiner to point out the specific page and line numbers in Sallberg that allegedly teach the "NS3/4A-antibody fusion." **The Examiner has not responded to this argument in this Office Action.**

Furthermore, Applicants have argued in the last response that Sallberg **teaches away from using the protease resistant protein**. In Example 3, it is shown that, while the protease resistant version of the NS3/4A mutant is still "comparable" to the wild-type NS3 protein in terms of immunogenicity, the NS3/4A fusion that is not protease resistant works better as an immunogen than the protease resistant version. "...the NS4A sequence and a functional proteolytic cleavage site between the NS3 and NS4A sequences provided for a more potent immune response" (emphasis added). *See* col. 3, Example 3 and Table 2. Because of this, Sallberg cannot be combined with the other cited references by relying on its alleged teaching of using **protease resistant protein**. **The Examiner also failed to address this argument.**

In summary, other than mere conclusory statements, the Office Action has failed to identify any reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. In addition, even assuming for the sake of argument that Whitcomb or Sallberg can be combined with Davis, the combined teaching still fails to teach or suggest all the limitations of the claims in each case. Finally, the Examiner has failed to respond to numerous arguments raised by Applicants, each tending to refute the foundation the Examiner relies upon to make the obviousness rejection. Therefore, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.

Double Patenting Rejection

The Office Action states that the provisional double patenting rejection will be withdrawn upon allowance when Applicants submit terminal disclaimer.

Applicants reiterate that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner

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Application No. 10/650,591
Amendment dated May 7, 2008
Reply to Office Action of January 23, 2008

Docket No.: COTH-P02-001

should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Applicants note that no claim has been issued in the co-pending application Nos. 10/792,498 and 10/650,592. Thus if the only rejection in the instant application is the provisional double patenting rejection, the Examiner should withdraw that rejection and permit the application to issue as a patent without requiring a terminal disclaimer.

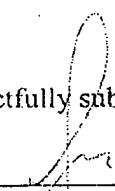
If conflicting claims are first allowed in the co-pending U.S. Application No. 10/792,498 or U.S. Application No. 10/650,592, and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, from which the undersigned is authorized to draw under Order No. COTH-P02-001.

Dated: May 7, 2008

Respectfully submitted,

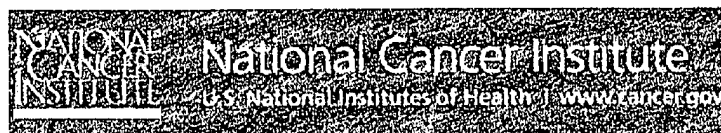
By 
Yu Lu, Ph.D., J.D.
Registration No.: 50,306
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant

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Definition of fusion protein - NCI Dictionary of Cancer Terms

Page 1 of 1

Exhibit A



In English | En español



Dictionary of Cancer Terms



In English | En español

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fusion protein (FYOO-zhun PROH-teen)

A protein created by joining two genes together. Fusion proteins may occur naturally or can be created in the laboratory for research.

Previous

Definitions:

functional magnetic resonance imaging, functioning tumor, fundus, fungating lesion, fungus

Next Definitions:

G-CSF, gabapentin, GAD, gadolinium texaphyrin, gadopentetate dimeglumine

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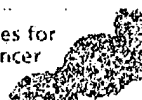
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Fusion protein - Wikipedia, the free encyclopedia

Page 1 of 2

Exhibit B

Fusion protein

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From Wikipedia, the free encyclopedia

Fusion proteins, also known as **chimeric proteins**, are proteins created through the joining of two or more genes which originally coded for separate proteins. Translation of this *fusion gene* results in a single polypeptide with function properties derived from each of the original proteins. *Recombinant fusion proteins* are created artificially by recombinant DNA technology for use in biological research or therapeutics. *Chimeric mutant proteins* occur naturally when a large-scale mutation, typically a chromosomal translocation, creates a novel coding sequence containing parts of the coding sequences from two different genes. Naturally occurring fusion proteins are important in cancer, where they may function as oncoproteins. The bcr-abl fusion protein is a well-known example of an oncogenic fusion protein, and is considered to be the primary oncogenic driver of chronic myelogenous leukemia.

Contents

- 1 Properties of fusion proteins
- 2 Recombinant fusion proteins
 - 2.1 Chimeric protein drugs
- 3 Naturally occurring fusion proteins
- 4 See also
- 5 External links

Properties of fusion proteins

The functionality of fusion proteins is made possible by the fact that many protein functional domains are *modular*. In other words, the linear portion of a polypeptide which corresponds to a given domain, such as a tyrosine kinase domain, may be removed from the rest of the protein without destroying its intrinsic enzymatic capability.

Recombinant fusion proteins

A **recombinant fusion protein** is a protein created through genetic engineering of a fusion gene. This typically involves removing the stop codon from a cDNA sequence coding for the first protein, then appending the cDNA sequence of the second protein in frame through ligation or overlap extension PCR. That DNA sequence will then be expressed by a cell as a single protein. The protein can be engineered to include the full sequence of both original proteins, or only a portion of either.

If the two entities are proteins, often linker (or "spacer") peptides are also added which make it more likely that the proteins fold independently and behave as expected. Especially in the case where the linkers enable protein purification, linkers in protein or peptide fusions are sometimes engineered with cleavage sites for proteases or chemical agents which enable the liberation of the two separate proteins. This technique is often used for identification and purification of proteins, by fusing a GST protein, FLAG peptide, or a hexa-his peptide (aka: a 6xhis-tag) which can be isolated using nickel or cobalt resins (affinity chromatography). Chimeric proteins can also be manufactured with toxins or anti-bodies attached to them in order to study disease development.

Chimeric protein drugs

Several drugs made from chimeric proteins are currently available for medical use. Several chimeric protein drugs are TNF α blockers, such as Etanercept, Infliximab, and Adalimumab.

Naturally occurring fusion proteins

Naturally occurring fusion genes are most commonly created when a chromosomal translocation replaces the terminal exons of one gene with intact exons from a second gene. This creates a single gene which can be transcribed, spliced, and translated to produce a functional fusion protein. Many important cancer-promoting oncogenes are fusion genes produced in this way.

Examples include:

- Gag-onc fusion protein
- Bcr-abl fusion protein

Exhibit C

THE DICTIONARY OF CELL & MOLECULAR BIOLOGY

JM Lackie & JAT Dow



The Dictionary of CELL AND MOLECULAR BIOLOGY

Third Edition

J. M. Lackie and J. A. T. Dow

*Yamanouchi Research Institute, Littlemore Park,
Oxford OX4 4SX, UK*

and

*University of Glasgow, IBLS, division of
Molecular Genetics, Glasgow G11 6NU, UK*

Contributing Authors

S. E. Blackshaw

C. T. Brett

A. S. G. Curtis

J. G. Edwards

A. J. Lawrence

G. R. Moores



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Molecular cell biology links the molecular life sciences with the rest of biology and medicine. The vocabulary is hence diverse with subject specific terms and many from the whole range of adjoining disciplines. The two previous editions of *The Dictionary of Cell Biology* gathered a broad working collection of widely used terms in cell and molecular biology, together with related expressions in genetics, neurobiology, together with related expressions in genetics, neurobiology, physiology, immunology and pathology.

The third edition builds on the foundations of its predecessors but in a unique manner. Preparation of this volume was influenced both by readers' comments and by usage of the Internet version of the second edition. Thus for the first time ever, this is a dictionary that reflects the demands made by users.

Over 2000 new entries bring the total to more than 7000 terms, each expertly explained and cross-referenced where necessary. The growing areas of molecular and neurobiology and the near completion of the Human Genome Project have attracted more detailed coverage. Biologists entering these territories will find this book extremely useful.

The Dictionary will serve equally as a handy reference, a companion to other reference texts, or a spelling and fact checker for students, research scientists and those engaged in ancillary activities, such as science journalists, and the curious lay readers.

It will find a place on the bookshelves of laboratories and libraries for many years to come. *The Times Higher Education Supplement*

It fills an undoubted gap and is stunningly up to date. *Biologist*

All the students seemed to find the dictionary of use and cries of "So that's what electroporation/vimentin/Kle now fragment is!" rang around the student's concourse. *TIBS*

A very useful reference book that every cell biologist should seriously consider purchasing and is a must for biology libraries. *Cell Biology International Reports*

The definitions are more comprehensive than one finds in most dictionaries and should help both students and research workers in other branches of biology. *Genetical Research*

Cover image courtesy of James T. Murray (Albert Einstein College of Medicine of Yeshiva University, NY USA). Image caption inside, page iv.



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elsewhere. Also of interest and utility because of the very low levels of repetitive DNA found in the genome.

fumagillin Naturally secreted antibiotic from *Aspergillus fumigatus* that inhibits endothelial cell proliferation and is therefore potentially anti-angiogenic.

fumarate A dicarboxylic acid intermediate in the Krebs cycle (*tricarboxylic acid cycle*). Can be derived from aspartate, phenylalanine and tyrosine for input to the Krebs cycle.

functional cloning (expression cloning) Strategy for cloning a desired gene that is based on some property (antigenicity, ligand binding, etc.) of the expressed gene. For example, a cDNA library could be produced in a eukaryotic *expression vector*, and transfected into a large number of cells. To identify a particular transport protein, a radiolabelled substrate could be added, and cells containing the protein of interest identified by radiography. The plasmid could then be recovered and the gene's sequence determined.

Fundulus heteroclitus The killifish. A teleost much used for the study of early embryonic development because the egg and embryo are transparent.

fura-2 A fluorescent dye, used in measurement of intracellular free calcium levels.

furin *Subtilisin*-like eukaryotic endopeptidase with substrate specificity for consensus sequence Arg-X-Lys/Arg-Arg at the cleavage site. Furin is known to activate the haemagglutinin of fowl plague virus and will cleave the HIV envelope glycoprotein (gp160) into two portions, gp120 and gp41, a necessary step in making the virus fusion-competent.

furosemide (frusemide) Potent diuretic that increases the excretion of sodium, potassium and chloride ions, and inhibits their resorption in the proximal and distal renal tubules.

furunculosis Disease of fish caused by *Aeromonas salmonicida*. Major problem in fish farms.

Fusarium mycotoxins Important fungal mycotoxin contaminants of various food products. Include zearalenone, *diax-toxyscirpenol*, T-2 toxin, neosolaniol monoacetate, deoxynivalenol, nivalenol, fumonisin B1, fumonisin B2, moniliformin, fusarenon-X, HT-2 toxin and β -zearalenol.

fushi tarazu (ftz) (Japanese for 'too few segments'); a *pair-rule* gene of *Drosophila*.

fusiform Tapered at both ends, like a spindle, though the current rarity of spindles makes this a somewhat unhelpful description.

fusin Lymphocyte surface protein originally described as being an essential cofactor for HIV bound to CD4 to fuse with and enter the cell, later shown to be a chemokine receptor (CXCR4 in the case of lymphotropic virus strains, CCR5 for myelotropic strains). Since FIV will infect CD4 cells it is possible that the chemokine receptor is the original binding site

and CD4 the coreceptor, rather than the converse.

fusion protein Protein formed by expression of a hybrid gene made by combining two gene sequences. Typically this is accomplished by cloning a cDNA into an *expression vector* in-frame with an existing gene, perhaps encoding, eg. β -galactosidase. See *GST fusion protein*.

futile cycles Any sequence of enzyme-catalysed reactions in which the forward and reverse processes (catalysed by different enzymes) are constitutively active. Frequently used to describe the cycle of phosphorylation and dephosphorylation of phosphatidyl inositol derivatives in cell membranes.

Fx Very small protein (5 kD) from platelets that binds to G-actin rendering it assembly-incompetent.

fyn A non-receptor *tyrosine kinase*, related to *src*.